

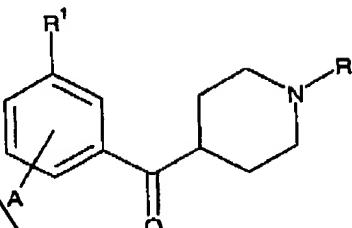
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WHAT IS CLAIMED IS:

1. A compound of Formula I:



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or a pharmaceutical acid addition salt thereof, where:

A is hydrogen, halo, -OR⁴, NH₂, or -CF₃;

R is hydrogen, C₁-C₄ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, or (C₁-C₈ alkyl)-Ar¹;

R¹ is -NH-R²-R³, hydroxy, -OSO₂Ar², or NH₂;

Ar, Ar¹, Ar², Ar³, and Ar⁴ are an optionally substituted phenyl or optionally substituted heteroaryl;

R² is -CO-, -CS-, or -SO₂-;

R³ is hydrogen, C₁-C₆ alkyl, optionally substituted with Ar³, -NR⁵R⁶, or OR⁵; provided

R³ is not hydrogen if R² is either -CS- or -SO₂-;

R⁴ is hydrogen, optionally substituted C₁-C₆ alkyl, or Ar; and

R⁵ and R⁶ are independently hydrogen, optionally substituted C₁-C₈ alkyl, or Ar⁴;

or R⁵ and R⁶ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piprazine, morpholine or thiomorpholine ring;

wherein substituted phenyl is phenyl mono-substituted with a substituent selected from the group consisting of halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, phenyl, benzoyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, (C₁-C₄ alkyl)S(O)_n, (C₁-C₄ alkyl)₂ amino, C₁-C₄ acyl, or two or three substituents independently selected from the group consisting of halo, nitro, trifluoromethyl, C₁-C₄ alkyl, and C₁-C₄ alkoxy;

n is 0, 1, or 2;

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~~heteroaryl is an aromatic or benzofused aromatic 5 or 6 membered ring containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;~~

~~substituted heteroaryl is heteroaryl substituted with up to three substituents selected from the group consisting of halo, cyano, nitro, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, (C₁-C₄ alkyl)-S(O)_n-, and phenyl-S(O)_n;~~

~~substituted alkyl is alkyl substituted from 1 to 3 times independently with a substituent selected from the group consisting of halo, hydroxy, phenyl, 2-phenylethylen-1-yl, diphenylmethyl, naphthyl, substituted phenyl, aryloxy, heterocycle, heteroaryloxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, phenyl(C₁-C₄ alkyl), substituted phenyl(C₁-C₄ alkyl), and benzofused C₄-C₈ cycloalkyl; and~~

~~heterocycle is aromatic or non-aromatic 5 or 6 membered ring containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, said ring being optionally benzofused and said ring or benzofused ring being optionally substituted with up to three substituents selected from the groups consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkyl, cyano, nitro, hydroxy, (C₁-C₄ alkyl)-S(O)_n-, and phenyl-S(O)_n.~~

2. The compound of Claim 1 wherein A is hydrogen.

A'

3. The compound of Claim 1 wherein R is methyl.

4. The compound of Claim 1 wherein R¹ is NH-R²-R³.

5. The compound of Claim 4 wherein R² is C=O.

6. The compound of Claim 5 wherein R³ is Ar³.

7. The compound of Claim 6 wherein Ar³ is 4-fluorophenyl.

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a'

8. The compound of Claim 7 wherein Ar³ is 4-fluorophenyl additionally mono- or disubstituted.

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9. The compound of Claim 8 wherein Ar³ is selected from the group consisting of 2-iodo-4-fluorophenyl, 2-bromo-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2,4-difluorophenyl, and 2-methyl-4-fluorophenyl, and 2,4,6-trifluorophenyl.

10. A pharmaceutical formulation comprising a compound of Formula I of Claim 1, or a pharmaceutical acid addition salt thereof, and a pharmaceutical carrier, diluent, or excipient.

11. A compound of Formula I of Claim 1 when used for activating 5-HT_{1F} receptors in a mammal.

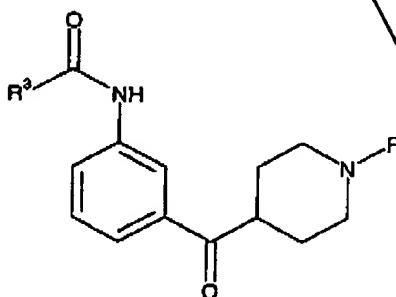
12. A compound of Formula I of Claim 1 when used for inhibiting neuronal protein extravasation in a mammal.

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13. The method according to Claim 11 where the mammal is a human.

14. A process of making the compounds of formula I(a):

I(a)



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~~wherein R³ is hydrogen, optionally substituted C₁-C₆ alkyl, Ar³, -NR⁵R⁶, or OR⁵;~~

~~R⁵ and R⁶ are independently hydrogen, optionally substituted C₁-C₆ alkyl, or Ar⁴; or R⁸ and R⁵ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring; and~~

~~Ar³ and Ar⁴ are independently an optionally substituted phenyl or optionally substituted heteroaryl;~~

~~wherein substituted phenyl is phenyl mono-substituted with a substituent selected from the group consisting of halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, phenyl, benzoyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, (C₁-C₄ alkyl)S(O)_n, (C₁-C₄ alkyl)₂ amino, C₁-C₄ acyl, or two or three substituents independently selected from the group consisting of halo, nitro, trifluoromethyl, C₁-C₄ alkyl, and C₁-C₄ alkoxy;~~

~~n is 0, 1, or 2;~~

~~heteroaryl is an aromatic or benzofused aromatic 5 or 6 membered ring containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;~~

~~substituted heteroaryl is heteroaryl substituted with up to three substituents independently selected from the group consisting of halo, cyano, nitro, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkyl, (C₁-C₄ alkyl)-S(O)_n-, and phenyl-S(O)_n;~~

~~substituted alkyl is alkyl substituted from 1 to 3 times independently with a substituent selected from the group consisting of halo, hydroxy, phenyl, 2-phenylethenyl, diphenylmethyl, naphthyl, substituted phenyl, aryloxy, heterocycle, heteroaryloxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, phenyl(C₁-C₄ alkyl), substituted phenyl(C₁-C₄ alkyl), and benzofused C₄-C₈ cycloalkyl;~~

~~heterocycle is aromatic or non-aromatic 5 or 6 membered ring containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, said ring~~

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being optionally benzofused and said ring or benzofused ring being substituted with up to three substituents selected independently from the groups consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkyl, cyano, nitro, hydroxy, (C₁-C₄ alkyl)-S(O)_n-, and phenyl-S(O)_n;- comprising:

- (a) protecting 4-benzoylpiperidine hydrochloride to form an N-protected 4-benzoylpiperidine hydrochloride;
- (b) nitrating the N-protected 4-benzoylpiperidine hydrochloride to form a mixture of N-protected 4-(mono nitrobenzoyl)piperidines;
- (c) deprotecting the N-protected 4-(mononitrobenzoyl)-piperidine mixture to form a mixture of 4-(mononitrobenzoyl)piperidines;
- (d) separating the 4-(3-nitrobenzoyl)piperidine from the mixture of 4-(mononitrobenzoyl)piperidines;
- (e) reducing the 4-(3-nitrobenzoyl)piperidine to form 4-(3-aminobenzoyl)piperidine; and
- (f) acylating the 4-(3-aminobenzoyl)piperidine.

15. The process of Claim 14 wherein steps a) and b) are combined.

16. The process of Claim 14 wherein the source of the protecting group of step a) is trifluoroacetic anhydride.

17. The process of Claim 14 wherein the source of the nitronium ion is ammonium nitrate.

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18. The process of any of Claim 16 wherein the source of the nitronium ion is ammonium nitrate.

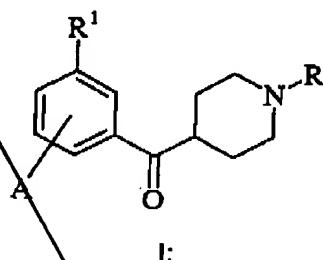
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19. The method according to Claim 12 where the mammal is a human.

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20. A method for treating migraine in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I:



or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, -OR⁴, NH₂, or -CF₃;

R is hydrogen, C₁-C₄ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, or (C₁-C₆ alkyl)-Ar¹;

R¹ is -NH-R²-R³, hydroxy, -OSO₂Ar², or NH₂;

Ar, Ar¹, Ar², Ar³, and Ar⁴ are an optionally substituted phenyl or optionally substituted heteroaryl;

R² is -CO-, -CS-, or -SO₂-;

R³ is hydrogen, optionally substituted C₁-C₆ alkyl, Ar³, -NR⁵R⁶, or OR⁵; provided R³ is not hydrogen if R² is either -CS- or -SO₂-;

R⁴ is hydrogen, optionally substituted C₁-C₆ alkyl, or Ar; and

R⁵ and R⁶ are independently hydrogen, optionally substituted C₁-C₈ alkyl, or Ar⁴; or R⁶ and R⁵ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

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A³*

21. The method according to Claim 20 where the mammal is a human.
22. The compound of Claim 5 where A is hydrogen and R is methyl.
23. The compound of Claim 6 where A is hydrogen and R is methyl.
24. The compound of Claim 7 where A is hydrogen and R is methyl.
25. The compound of Claim 6 where R¹ is NH-R²-R³, R² is C=O and R³ is substituted halophenyl.